Most Recent Modification: February 2016

The iPLEDGE Program

The Pharmacist Guide For the iPLEDGE Program

The resource to help the pharmacist understand and comply with the iPLEDGE Program for isotretinoin therapy

Isotretinoin must not be used by female patients who are or may become pregnant. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking isotretinoin in any amount, even for a short period of time. Potentially any fetus exposed during pregnancy can be affected. There are no accurate means of determining whether an exposed fetus has been affected.

IMPORTANT NOTICE

Use only isotretinoin products approved by the US Food and Drug Administration.

Obtain isotretinoin prescriptions *only* from pharmacies that are licensed in the United States and are registered with and activated in the iPLEDGE Program.

iPLEDGE™

Committed to Pregnancy Prevention

Reference ID: 3882660

The Pharmacist Guide For the iPLEDGE Program

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For iPLEDGE Program Information

Call Center hours: Monday through Saturday, 9AM–12AM (midnight) EST

1-866-495-0654

www.ipledgeprogram.com

CONTRAINDICATIONS AND WARNINGS

Isotretinoin must not be used by female patients who are or may become pregnant. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking isotretinoin in any amount, even for short periods of time. Potentially any fetus exposed during pregnancy can be affected. There are no accurate means of determining whether an exposed fetus has been affected.

Birth defects which have been documented following isotretinoin exposure include abnormalities of the face, eyes, ears, skull, central nervous system, cardiovascular system, and thymus and parathyroid glands. Cases of IQ scores less than 85 with or without other abnormalities have been reported. There is an increased risk of spontaneous abortion, and premature births have been reported.

Documented external abnormalities include: skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia); facial dysmorphia; cleft palate. Documented internal abnormalities include: CNS abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular abnormalities; thymus gland abnormality; parathyroid hormone deficiency. In some cases death has occurred with certain of the abnormalities previously noted.

If pregnancy does occur during treatment of a female patient who is taking isotretinoin, isotretinoin must be discontinued immediately, and she should be referred to an Obstetrician-Gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Special Prescribing Requirements

Because of isotretinoin's teratogenicity and to minimize fetal exposure, isotretinoin is approved for marketing only under a special restricted distribution program approved by the Food and Drug Administration. This program is called iPLEDGE™. Isotretinoin must only be prescribed by prescribers who are registered and activated with the iPLEDGE Program. Isotretinoin must only be dispensed by a pharmacy registered and activated with the iPLEDGE Program, and must only be dispensed to patients who are registered and meet all the requirements of the iPLEDGE Program (see **PRECAUTIONS**).

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS.**

Reference ID: 3882660

ABOUT ISOTRETINOIN

Isotretinoin is used to treat severe recalcitrant nodular acne. Isotretinoin belongs to a class of drugs known as retinoids, commonly understood to include all natural and synthetic analogues of vitamin A. Therapy with isotretinoin should not be undertaken before conventional treatment has been tried first, including the use of systemic antibiotic therapy, and the patient has been fully counseled about the warnings and precautions in the isotretinoin package insert.

Isotretinoin is teratogenic and must not be used by pregnant women. Women should not become pregnant while taking isotretinoin or for 1 month after therapy is discontinued. A patient who becomes pregnant during treatment should stop taking isotretinoin and immediately contact her prescriber.

Isotretinoin use is associated with other potentially serious adverse events as well as more frequent, but less serious side effects. More frequent, less serious side effects include cheilitis, dry skin, skin fragility, pruritus, epistaxis, dry nose and dry mouth, and conjunctivitis.

Serious Adverse Event Warnings include psychiatric disorders* (depression, psychosis and, rarely, suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviors). Prescribers should read the brochure *Recognizing Psychiatric Disorders in Adolescents and Young Adults: A Guide for Prescribers of Isotretinoin*. Prescribers should be alert to the warning signs of psychiatric disorders to guide patients to receive the help they need. Therefore, prior to initiation of isotretinoin therapy, patients and family members should be asked about any history of psychiatric disorder, and at each visit during therapy patients should be assessed for symptoms of depression, mood disturbance, psychosis, or aggression to determine if further evaluation may be necessary.

Other Serious Adverse Events include pseudotumor cerebri; pancreatitis; hyperlipidemia; hearing impairment*; hepatotoxicity; inflammatory bowel disease; skeletal changes† (bone mineral density changes, hyperostosis, premature epiphyseal closure); and visual impairment (corneal opacities, decreased night vision).

Patients should be reminded to read the Medication Guide, distributed by the pharmacist at the time the isotretinoin is dispensed as required by law.

* No mechanism of action has been established for these events

† The use of isotretinoin in patients 12 to 17 should be given careful consideration especially when a known metabolic or structural bone disease exists

Pregnancy After Isotretinoin Therapy

The terminal elimination half-life of isotretinoin varies but is generally within 10 to 20 hours. The elimination half-life of one of the isotretinoin metabolites, 4-oxoisotretinoin, is approximately 25 hours. Since plasma elimination is host dependent, prescribers should warn patients not to become pregnant for 1 month post treatment. Women who become pregnant during this month should be counseled as to the outcome data. In 1989, Dai et al reported the results of an epidemiologic study of pregnancies that occurred in women who conceived after discontinuing isotretinoin.[1] They studied women from 5 days to more than 60 days between the last dose of isotretinoin and conception. The incidence of birth defects in former isotretinoin patients was not significantly different from the rate in the general population.

Isotretinoin is found in the semen of male patients taking isotretinoin, but the amount delivered to a female partner would be about 1 million times lower than an oral dose of 40 mg. While the no-effect limit for isotretinoin-induced embryopathy is unknown, 20 years of postmarketing reports include 4 with isolated defects compatible with features of retinoid-exposed fetuses; however, 2 of these reports were incomplete, and 2 had other possible explanations for the defects observed.

Birth Defects

There is an extremely high risk that a deformed infant will result if pregnancy occurs while female patients are taking isotretinoin in any amount even for short periods of time. Potentially, any fetus exposed during pregnancy can be affected. Not every fetus exposed to isotretinoin has resulted in a deformed child. However, there are no accurate means of determining which fetus has been affected and which fetus has not been affected.

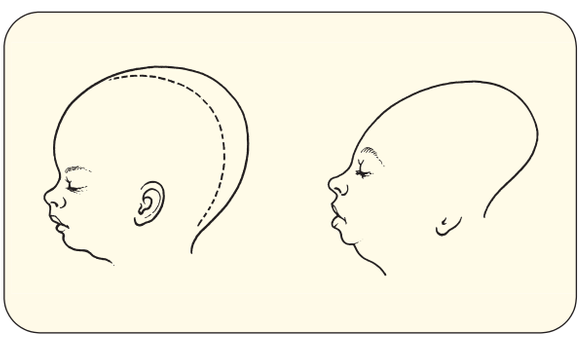
When isotretinoin is taken during pregnancy, it has been associated with fetal malformations, and there is an increased risk for spontaneous abortions and premature birth. **The following human fetal abnormalities have been documented.**

External abnormalities

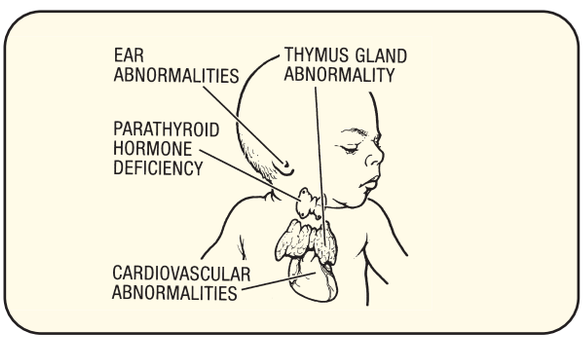
Skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia); facial dysmorphia; cleft palate.

Internal abnormalities

CNS abnormalities including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit; cardiovascular abnormalities; thymus gland abnormalities; parathyroid hormone deficiencies. In some cases death has occurred with certain of the abnormalities noted.



Line drawing represents the possible abnormalities of the low-set, deformed, or absent ears; wide-set eyes; depressed bridge of nose; enlarged head; and small chin.



Line drawing represents the possible abnormalities of the brain, heart, and thymus gland that may occur.

THE iPLEDGE PROGRAM

Because of isotretinoin's teratogenicity and to minimize fetal exposure, isotretinoin is approved for marketing only under a special restricted distribution program approved by the Food and Drug Administration. This program is called iPLEDGE.

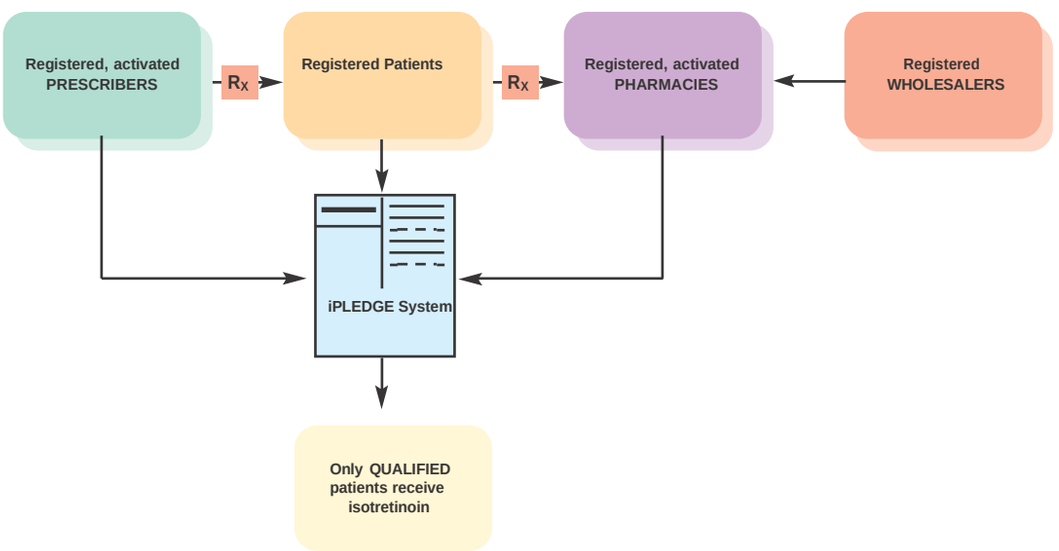
The iPLEDGE Program is a single, shared Risk Evaluation and Mitigation Strategy (REMS) program for prescribing and dispensing all isotretinoin products (brand and generic products) and includes a pregnancy registry.

Isotretinoin must only be prescribed by prescribers who are registered and activated with the iPLEDGE Program. Isotretinoin must only be dispensed by a pharmacy registered and activated with the iPLEDGE Program, and must only be dispensed to patients who are registered and meet all the requirements of the iPLEDGE Program (see PRECAUTIONS).

The goals of the iPLEDGE Program are to prevent fetal exposure to isotretinoin and to inform prescribers, pharmacists, and patients about isotretinoin's serious risks and safe-use conditions.

The iPLEDGE Program is a computer-based risk management system that uses verifiable, trackable links between prescriber, patient, pharmacy, and wholesaler to control prescribing, using, dispensing, and distribution of isotretinoin.

The trackable links of the iPLEDGE Program



Non-Compliance Action Policy (NCAP)

The Non-Compliance Action Policy was implemented to monitor compliance, address deviations, and institute appropriate corrective actions to improve minimization of drug exposure during pregnancy and compliance with elements to assure safe use under the iPLEDGE Program. The NCAP sets forth the principles by which Non-Compliance by iPLEDGE Program stakeholders will be evaluated. The NCAP can be found on the iPLEDGE Program website at www.ipledgeprogram.com

Key Features Of The iPLEDGE Program

The iPLEDGE Program has specific requirements for prescribers, patients, pharmacists, and wholesalers. Here is an overview:

- The iPLEDGE Program system tracks and verifies critical program elements that control access to isotretinoin.
- Only prescribers registered with and activated in the iPLEDGE Program can prescribe isotretinoin.
- Prescribers must ensure that all patients—and specifically female patients of reproductive potential—meet the requirements to be registered in the iPLEDGE Program.
- Prescribers and patients must enter required information (i.e., pregnancy test results, 2 forms of contraception used, confirmation of patient counseling) in the iPLEDGE Program system for patients to be qualified to receive a prescription.
- Only patients who are registered by prescribers in the iPLEDGE Program can receive isotretinoin.
- Only pharmacies registered with and activated in the iPLEDGE Program can dispense isotretinoin.
- Pharmacists must access the iPLEDGE Program system to receive authorization to fill and dispense every prescription.
- Manufacturers will only ship to iPLEDGE-registered entities (e.g., direct vendor pharmacies, wholesalers).
- Wholesalers must register annually in the iPLEDGE Program. A registered wholesaler may distribute only FDA-approved isotretinoin product.
- Only wholesalers registered with the iPLEDGE Program can distribute isotretinoin. (See page 9 for information on how to find a registered wholesaler.)
- Registered wholesalers can only ship to wholesalers registered in the iPLEDGE Program with prior written consent from the manufacturer or pharmacies licensed in the US and registered and activated in the iPLEDGE Program.
- Telephone, fax, and electronic transmission (e.g., e-mail) prescriptions are permitted in the iPLEDGE Program.

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS.**

PHARMACIES AND THE iPLEDGE PROGRAM

The iPLEDGE Program includes specific requirements that pharmacies must follow in order to dispense isotretinoin. These include:

- Reviewing and abiding by the Non-Compliance Action Policy (NCAP) (www.ipledgeprogram.com)
- Designating a Responsible Site Pharmacist (*see page 11*)
- Following the procedures to fill and dispense prescriptions (*see page 15*)

Key Information For Pharmacists

- **The Responsible Site Pharmacist must register and activate the pharmacy** in the iPLEDGE Program system.
- **The dispensing pharmacist must get authorization and a Risk Management Authorization (RMA) number** before filling and dispensing prescriptions.
- **Upon receiving authorization, the dispensing pharmacist can fill and dispense a prescription** for a maximum 30-day supply of isotretinoin.
- **Upon authorization, the iPLEDGE Program system** provides the RMA number to the dispensing pharmacist. The pharmacist should document the RMA number.
- **Upon authorization, the iPLEDGE Program system provides a "Do Not Dispense To Patient After"** date to the dispensing pharmacist. This date is calculated as 30 days from the office visit for male patients and females of non-reproductive potential, or 7 days from the pregnancy test date for female patients of reproductive potential. It is recommended that the pharmacist write the date on the sticker and put the sticker on the prescription bag.
- Patients who present a prescription beyond this date will not be authorized in the iPLEDGE Program system to receive isotretinoin.
- **Prescriptions must be obtained by the patient no later than the "Do Not Dispense To Patient After" date, and if not obtained, then the RMA must be reversed in the iPLEDGE Program system and the product returned to inventory.**
- **The iPLEDGE Program system** only authorizes filling and dispensing prescriptions when patients have met the qualification criteria in the system.
- **Prescriptions** that are more than 30 days beyond the date of the office visit (for male patients and females of non-reproductive potential) or more than 7 days beyond the pregnancy test date (for females of reproductive potential) will not be authorized by the iPLEDGE Program system.
- **No automatic refills** are permitted.
- Telephone, fax, and electronic transmission (e.g., e-mail) prescriptions are permitted in the iPLEDGE Program.
- **Isotretinoin** comes in blister packs of 10 capsules. The pharmacist cannot break a blister pack.
- An isotretinoin Medication Guide must be given to the patient each time isotretinoin is dispensed, as required by law.

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS.**

Reference ID: 3882660

A complete list of FDA-approved isotretinoin products that may be prescribed and dispensed may be found by calling 1-866-495-0654 or via www.ipledgeprogram.com.

About Authorization Criteria

Prior to each prescription, the prescriber and patient must enter required patient information into the iPLEDGE Program system. The pharmacist is not responsible for entering this information. When the pharmacist begins the authorization process, the system automatically checks this information to ensure that the patient has met the criteria to receive a prescription. (See page 20 for the specific criteria.)

THE iPLEDGE Program WEB SITE AND PHONE SYSTEM

The pharmacist can access the iPLEDGE Program system via the program web site and automated phone system:

- Web site: **www.ipledgeprogram.com**
- Phone system: **1-866-495-0654**

The iPLEDGE Program system is used for:

- Activation of the pharmacy registration
- Authorization to fill and dispense prescriptions
- Reversal of approved prescriptions
- Ordering additional copies of *The Pharmacist Guide For the iPLEDGE Program* and patient and professional educational materials
- Finding a wholesaler registered in the iPLEDGE Program
- Finding a pharmacy participating in the iPLEDGE Program
- FAQ's (Frequently Asked Questions)

To log in to either the web site or the phone system, the dispensing pharmacist needs the pharmacy username and password supplied upon registration. The pharmacy's Responsible Site Pharmacist can supply this information.

It is important that the Responsible Site Pharmacist does not forget the iPLEDGE Program username, password, and date of personal significance for the pharmacy. All of these items should be communicated to other pharmacists working at the pharmacy.

(Note: Date of Personal Significance is chosen by you, and can be any date that is easy for you to remember)

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS.**

To Review And Order Materials

You can order additional program materials using either the web site or the phone system as follows:

1. After logging on to the web site, there are two ways to order materials:
   a. Using the navigation menu on the left side of the page, select the “Order Materials” button.

      OR

   b. Using the navigation menu on the left side of the page choose “Pharmacy Information.” In the “View Information Online” section, select “To Order Educational Materials, please click here.”
2. In the phone system, log in and select the option to “Request Program Information.” Additional bag stickers can also be ordered using this process.

To Find A Registered Wholesaler

On the web site, log in and choose “Find Wholesaler” in the left navigation. A list of registered wholesalers and distributors will be presented.

THE RESPONSIBLE SITE PHARMACIST

Each pharmacy in the iPLEDGE Program must designate a pharmacist as the Responsible Site Pharmacist. The Responsible Site Pharmacist is the point of contact for the pharmacy and the iPLEDGE Program. The Responsible Site Pharmacist performs the following tasks:

- Registers the pharmacy with the iPLEDGE Program
- Activates the pharmacy registration initially and annually; attests to program requirements
- Trains all pharmacists who participate in the filling and dispensing of isotretinoin prescriptions and keeps a log or record of the staff who have been trained
- Ensures that all pharmacy staff using iPLEDGE are aware of the pharmacy's username, password and date of personal significance for the iPLEDGE Program System.

Registration

The Responsible Site Pharmacist registers the pharmacy in the iPLEDGE Program. Only one registration is needed for each pharmacy. After the Responsible Site Pharmacist registers the pharmacy, the pharmacy will receive a system password by mail. The NCPDP number is the username for the entire pharmacy.

Activation

Before a pharmacist can fill and dispense prescriptions for isotretinoin, the Responsible Site Pharmacist must activate the registration in the iPLEDGE Program system. The program activation expires annually. The Responsible Site Pharmacist, representing the pharmacy, must activate the automated registration annually to continue ordering, filling, and dispensing isotretinoin. If your activation expires, and you do not intend to reactivate, you must return all unused isotretinoin immediately to the manufacturer or delegate.

The iPLEDGE Program system will report the expiration date of a pharmacy's registration. To retrieve this information on the web site, log in and choose "My Program Status" on the left navigation; in the phone system, log in and select the option to hear "Current Program Status."

Review *The Pharmacist Guide For the iPLEDGE Program* to ensure an understanding of the program. Activation requires attesting to the following statements in the iPLEDGE Program system:

- I know the risk and severity of fetal injury/birth defects from isotretinoin.
- I will train all pharmacists, who participate in the filling and dispensing of isotretinoin prescriptions, on the iPLEDGE Program requirements.

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS.**

- I will comply and seek to ensure all pharmacists who participate in the filling and dispensing of isotretinoin prescriptions comply with the iPLEDGE Program requirements described in the booklet entitled *The Pharmacist Guide For the iPLEDGE Program*, specifically the "Key Information for Pharmacists" section including the following dispensing information:
    - **Prescriptions must be obtained up no later than the "Do Not Dispense To Patient After" date, and if not obtained, then the RMA must be reversed in the iPLEDGE Program system and the product returned to inventory.**
- I will only obtain isotretinoin product from only iPLEDGE-registered wholesalers.
- I will not sell, buy, borrow, loan, or otherwise transfer isotretinoin in any manner to or from another pharmacy.
- I will return to the manufacturer (or delegate) any unused product if registration is revoked by the manufacturer or if the pharmacy chooses to not reactivate annually.
- I will not fill isotretinoin for any party other than a qualified patient.

Procedures For Activating In The iPLEDGE System

Access the iPLEDGE Program system to activate the pharmacy's registration via the web site, **www.ipledgeprogram.com**, or the automated phone system, **1-866-495-0654**. Both the web site and the phone system provide prompts to log in and complete the initial activation. Identification in either system requires the username (NCPDP number) and the password received upon registration.

The web site is the faster and easier way to access the system. After initial activation, a pharmacy must re-activate at least annually to remain active in the iPLEDGE Program.

The iPLEDGE Program system will display the "Activate" button on the Pharmacy home page when the activation for a pharmacy is nearing expiration. However, a pharmacy can re-activate at any time using the "Activate Pharmacy Registration" button on the left-hand navigation menu on all pages.

The system requires setting the pharmacy's Date of Personal Significance.

- The date of personal significance is a date that is easily remembered and will be used to verify the pharmacy's identity if required by the iPLEDGE Program system or if the pharmacy's password is lost.
- The same date of personal significance will be used by all pharmacists in the pharmacy when contacting the iPLEDGE Call Center.
- **The date of personal significance should be a date that will be known by all the pharmacists at the pharmacy.**
- It is important that you remember the selected date of personal significance. It is used to verify Pharmacy identity for some functions within the iPLEDGE Program, as well as to obtain assistance from the iPLEDGE Call Center. The

selected date should be communicated to other pharmacists in your pharmacy that will be using the iPLEDGE Program.

- If you change the date of personal significance for your pharmacy, you should communicate this change to others at your pharmacy that will be using the iPLEDGE Program System.

Using the web site

The Responsible Site Pharmacist:

1. Logs in by entering the pharmacy username (NCPDP number) and password.
2. Changes the pharmacy password and sets the date of personal significance.
3. Selects "Activate Pharmacy Registration" from the Pharmacy home page. The system will provide prompts to complete the activation process. If the current activation for a pharmacy is nearing expiration, the Pharmacy home page will prominently display a direct link to re-activate.

Using the automated phone system

The Responsible Site Pharmacist:

1. At the main menu, selects the option to log in and follows the prompts to enter the pharmacy username (NCPDP number) and password.
2. Changes the pharmacy password and sets the date of personal significance.
3. At the pharmacy menu, selects the option to begin the activation process

Training Pharmacists

The Responsible Site Pharmacist is responsible for the training, and the documentation of training, of all pharmacists in a registered pharmacy. The pharmacy's standard operating procedures for training may be followed in training pharmacists on the iPLEDGE Program requirements.

The training objectives for all dispensing pharmacists include:

- Knowing about isotretinoin teratogenicity and the contraception and program requirements of the iPLEDGE Program
- Being able to access the iPLEDGE Program system and obtain authorization to fill and dispense a prescription
- Correctly using the RMA number and **"Do Not Dispense To Patient After"** date

Training begins by providing *The Pharmacist Guide For the iPLEDGE Program* to all pharmacists. Additional copies can be requested through the automated system.

The Responsible Site Pharmacist should review the following sections with each pharmacist after he/she has read the material:

- Isotretinoin teratogenicity and measures to reduce fetal exposure (*see "About Isotretinoin," page 3*)

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS.**

- Accessing the iPLEDGE Program system via web site and phone system, using username (NCPDP number) and system password (*see page 13*)
- iPLEDGE Program procedures for filling and dispensing prescriptions (*see page 15*)
- Time limitations on dispensing (*see page 16*)
- Prescription bag sticker requirements (*see page 16*)
- Patient qualification criteria (*see page 17*)
- Effective primary and secondary forms of contraception (*see page 19*)
- Additional contraception information and counseling about pregnancy (*see page 22*)

After reviewing the material, the Responsible Site Pharmacist should:

- Review the steps with the pharmacist for accessing the iPLEDGE Program system and the procedures for obtaining authorization to fill a prescription (*see page 15*)
- Ensure that pharmacists have the date of personal significance, username, and password necessary to log in to the iPLEDGE Program system
- Record the date of training, have the pharmacist sign a log or record of training, and co-sign this training record; verification of training records may be requested and reviewed as part of the iPLEDGE Program

To Change The Responsible Site Pharmacist

The pharmacy can change its designated Responsible Site Pharmacist at any time. The new Responsible Site Pharmacist or the former Responsible Site Pharmacist can make the change on the automated phone line, **1-866-495-0654**.

The new Responsible Site Pharmacist:

- Selects the option to continue in English
    - Pharmacy support is only available in English
- Logs in with the pharmacy's username and password
- Selects #0 to transfer to the Call Center, then presses 1 at the prompt
- Selects the option for pharmacies
- The Responsible Site Pharmacist will be connected with an operator, who will assist with the change.
- The new Responsible Site Pharmacist must re-activate the pharmacy in the iPLEDGE Program (for activation information, see page 12)
    - If your activation expires, and you do not intend to reactivate, you must return all unused isotretinoin immediately to the manufacturer or delegate.

PROCEDURE FOR FILLING AND DISPENSING PRESCRIPTIONS

Access the iPLEDGE system

The dispensing pharmacist:

- Accesses the iPLEDGE Program system via the web site, **www.ipledgeprogram.com** or the automated phone system, **1-866-495-0654**
- Logs in using the pharmacy username (NCPDP number) and the pharmacy password
  - On the web site, chooses "Fill Prescriptions" from the left navigation
  - In the phone system, selects the option to "Obtain Approval to Fill or Reverse a Prescription"
- Enters the patient ID number from the patient ID card
- Enters the patient's date of birth

Confirm patient qualification and obtain authorization

- The iPLEDGE Program system automatically checks patient qualification criteria for you.
- Prescriptions will be authorized only for those patients who meet all criteria.
- If authorized to fill and dispense, the pharmacist enters the:
  - NDC Code
  - Number of days to be dispensed
  - Amount dispensed
- System provides:
  - An RMA number to be documented
  - A **"Do Not Dispense To Patient After"** date. It is recommended that the pharmacist write the date on the sticker and put the sticker on the prescription bag.

Additional strengths for the prescription to achieve the desired dosage can be entered by the pharmacist immediately after the prescription is authorized. If not added immediately, the prescription must be reversed and then re-authorized if the dosage is not correct.

- The pharmacist may proceed with normal insurance adjudication only if the iPLEDGE Program system has authorized dispensing.
- The pharmacist may not proceed with normal insurance adjudication and may not dispense isotretinoin if dispensing is not authorized in the iPLEDGE Program system.
- If not authorized to fill and dispense:
  - The system will provide information or instructions for the patient (e.g., "Please contact your doctor")

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS.**

Reference ID: 3882660

Dispense the prescription

- Only FDA-approved products may be dispensed.
- The system will automatically calculate and provide the **"Do Not Dispense To Patient After"** date to the pharmacist. The pharmacist must not dispense the prescription after this date.
- A maximum 30-day supply of isotretinoin may be dispensed.
- Refills are not allowed. Monthly continuation of therapy requires the patient to satisfy the iPLEDGE Program requirements to obtain a new prescription.

Prescription bag stickers

- The bag sticker has space for the **"Do Not Dispense To Patient After"** date.
- The iPLEDGE Program system provides the **"Do Not Dispense To Patient After"** date.
- The pharmacist should document the date. It is recommended that the pharmacist write the date on the sticker and put the sticker on the prescription bag.
- Additional stickers can be ordered. (*see page 10*)

DO NOT DISPENSE ISOTRETINOIN AFTER THE DATE ON THE BAG STICKER

Non-dispensed prescriptions

If the prescription is not dispensed for any reason (e.g., the patient did not obtain, dispense date expired, third party did not authorize payment, etc.) the authorization to dispense must be reversed in the system. The pharmacist must log in to the web site and select "Reverse Prescription" or call the iPLEDGE Program at **1-866-495-0654**, log in, and select the option to "Obtain Approval to Fill or Reverse a Prescription," or

iPLEDGE PROGRAM GENERAL INFORMATION

The following section covers general aspects of the iPLEDGE Program.

Determining Reproductive Potential Of Female Patients

The prescriber must determine if a female patient is of reproductive potential before registering the patient in the iPLEDGE Program.

The definition of a female of reproductive potential is a nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy, or documented ovarian failure. This definition includes a young woman who has not yet started menstruating.

A woman who has had a tubal sterilization is considered a female of reproductive potential in the iPLEDGE Program.

Definition of menopause

Menopause can be assumed to have occurred in a woman when there is either:

1. Appropriate medical documentation of prior complete bilateral oophorectomy (i.e., surgical removal of the ovaries, resulting in "surgical menopause" and occurring at the age at which the procedure was performed), OR
2. Permanent cessation of previously occurring menses as a result of ovarian failure with documentation of **hormonal deficiency** by a certified healthcare provider (i.e., "spontaneous menopause," which occurs in the United States at a mean age of 51.5 years).

Hormonal deficiency should be properly documented in the case of suspected spontaneous menopause as follows:

1. If age >54 years and with the absence of normal menses: Serum FSH (Follicle Stimulating Hormone) level elevated to within the post-menopausal range based on the laboratory reference range where the hormonal assay is performed;
2. If age <54 years and with the absence of normal menses: Negative serum or urine - HCG with concurrently elevated serum FSH (Follicle Stimulating Hormone) level in the post-menopausal range, depressed estradiol (E2) level in the post-menopausal range, and absent serum progesterone level, based on the laboratory reference ranges where the hormonal assays are performed.

All Patients

To receive isotretinoin, all patients must meet all of the following conditions:

1. ***Must*** be registered with the iPLEDGE Program by the prescriber
2. ***Must*** understand that severe birth defects can occur with the use of isotretinoin by female patients
3. ***Must*** be reliable in understanding and carrying out instructions

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS.**

4. ***Must*** sign a Patient Information/Informed Consent (for all patients) form that contains warnings about the potential risks associated with isotretinoin
5. ***Must*** obtain the prescription within their prescription window as follows:
   - Male patients and female patients who cannot get pregnant, prescriptions must be obtained within the 30-day prescription window, counting the office visit as DAY 1.
   - Female patients who can get pregnant, prescriptions must be obtained within the 7-day prescription window, counting the day of the blood draw or urine sample as DAY 1.
6. ***Must*** not donate blood while on isotretinoin and for 1 month after treatment has ended
7. ***Must*** not share isotretinoin with anyone, even someone who has similar symptoms

All patients should understand that refills are not allowed. Patients can only receive a maximum of 30-day supply of isotretinoin per prescription. For each prescription, continuation of therapy requires the patient to satisfy the iPLEDGE Program requirements to obtain a new prescription. The prescriber must also counsel the patient each month about the iPLEDGE Program requirements and then confirm via the iPLEDGE Program automated system that this counseling occurred.

Females Of Reproductive Potential

Once the prescriber decides to pursue qualification of the patient, a female of reproductive potential must follow these steps.

1. Females of reproductive potential ***must*** have had 2 negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial isotretinoin prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for isotretinoin. There is a 30-day wait period where the patient must be on two forms of birth control simultaneously. The second pregnancy test (a confirmation test) must be done in a CLIA-certified laboratory. The interval between the 2 tests must be at least 19 days.
   - For patients with regular menstrual cycles, the second pregnancy test must be done during the first 5 days of the menstrual period immediately preceding the beginning of isotretinoin therapy and after the patient has used 2 forms of contraception for 1 month.
   - For patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding, the second pregnancy test must be done immediately preceding the beginning of isotretinoin therapy and after the patient has used 2 forms of contraception for 1 month.
   - The patient must be using their two forms of birth control for at least 30 days prior to beginning to take isotretinoin, and their second pregnancy test must occur after this 30-day period is complete.
2. The patient must sign the Patient Information/Informed Consent (for all patients) form and the Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant) form.
3. The patient must select and commit to use 2 forms of effective contraception together, at least 1 of which must be a primary form, unless continuous abstinence is chosen. Patients must use 2 forms of effective contraception for at least 1 month prior to initiation of isotretinoin therapy, during isotretinoin therapy, and for 1 month after discontinuing isotretinoin therapy.

Requirements For Each Prescription

In addition to the requirements for all patients, the female patient of reproductive potential has additional requirements. Prior to each prescription, they must have a negative result from a urine or serum pregnancy test. A pregnancy test must be repeated, in a CLIA-certified laboratory, prior to the female patient receiving each prescription. A pregnancy test must also be obtained at the end of therapy (after the last dose) and 1 month after the last dose. Before each prescription, the iPLEDGE Program also requires monthly counseling about contraception and behaviors associated with an increased risk of pregnancy.

In addition to their required doctor appointments, females of reproductive potential must also report their 2 forms of birth control in the iPLEDGE Program system and answer questions about the iPLEDGE Program and pregnancy prevention.

Effective forms of contraception

Effective forms of contraception include both primary and secondary forms of contraception.

Primary forms	Secondary forms
• Tubal sterilization • Partner's vasectomy • Intrauterine device • Hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring)	*Barrier forms (always used with spermicide)* • Diaphragm • Cervical cap *Barrier form (used with or without spermicide)* • Male latex condom *Others:* • Vaginal sponge (contains spermicide)

Unacceptable forms of contraception

- Progesterone-only "mini-pills"
- Female condoms
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield‡

‡ A cervical shield should not be confused with a cervical cap, which is an effective secondary form of contraception

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS.**

Abstinence

For this program, all females of reproductive potential must fully commit to pregnancy prevention. Abstinence without appropriate contraception is not recommended for patients in the iPLEDGE Program who are or have been sexually active. Abstinence may be appropriate when it is a lifestyle choice (e.g., religious practice) and not just a social circumstance (e.g., not having a current partner). If, after counseling, a sexually active patient chooses abstinence without contraception, she must understand that isotretinoin is not recommended for any female of reproductive potential who cannot or will not follow the contraceptive requirements of the iPLEDGE Program. All females of reproductive potential must receive contraception counseling.

Patient Criteria For Authorization To Fill And Dispense

This is the information that must be entered by prescribers and patients into the iPLEDGE Program system for all patients and, specifically, for females of reproductive potential. This is the information the system uses to authorize filling a prescription and to provide the RMA number and the **"Do Not Dispense To Patient After"** date.

All patients

Prescriber confirms that:

- The patient is registered with the iPLEDGE Program
- The patient was counseled about the iPLEDGE Program requirements

Females of reproductive potential

Prescriber:

- Confirms that the patient was counseled about the iPLEDGE Program contraception requirements
- Enters the 2 forms of contraception that the patient is using
- Enters pregnancy test results to start the 7-day prescription window, counting the date of the specimen collection as DAY 1.

Patient:

- Correctly answers the questions about pregnancy prevention and the iPLEDGE Program
- Enters the 2 forms of contraception she is using

The primary form of contraception reported by both the prescriber and the patient must match.

Note: The system will automatically provide the pharmacist with the "Do Not Dispense To Patient After" date.

Note: the following is provided to the pharmacist for information purposes only. No action is required by the pharmacist for a patient to fulfill the requirements of the iPLEDGE Program and become qualified to obtain a prescription.

Reference ID: 3882660

All patients have a specific period of time in which they can obtain their prescription. This is called the "prescription window" and its start and end dates depend on the type of patient, as

Female patients who can get pregnant…	Male patients and female patients who cannot get pregnant…
The prescription window is 7 days and starts on the date that the urine or blood sample is taken for a pregnancy test. This date is counted as DAY 1. To determine the end date of their 7-day prescription window, these patients should add 6 days to the date of the blood or urine sample being taken.	The prescription window is 30 days and starts on the date that the prescriber enters as the date of the office visit. This date is counted as DAY 1. To determine the end date of their 30-day prescription window, these patients should add 29 days to the date of their office visit.

After 11:59 p.m. Eastern Time on the last day of the prescription window, the prescription can no longer be obtained and the patient must start the process over to get a new prescription window.*

* There are generally no restrictions regarding the timing of office visits. One notable exception is that females of reproductive potential who do not obtain their first month of therapy prescription in their first 7-day prescription window, must wait at least 19 days from their most recent pregnancy test until getting their next pregnancy test. **This is based on the requirement that the most recent pregnancy test prior to beginning therapy must be conducted in the first 5 days of her menstrual cycle.**

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS.**

Reference ID: 3882660

ADDITIONAL CONTRACEPTION INFORMATION

The iPLEDGE Program has *The iPLEDGE Program Prescriber Contraception Counseling Guide* available. This is the professional companion piece to the patient's *iPLEDGE Program Birth Control Workbook*. Copies can be requested through the iPLEDGE Program system. (See page 10 for instructions.)

Patients can also be directed to the phone system for confidential birth control information. They can call **1-866-495-0654**, log in, and select the option to hear "Confidential Birth Control Information."

The following subjects are covered:

1. Isotretinoin and Birth Defects
2. Sex, Pregnancy, and Birth Control
3. Different Methods of Birth Control
4. Emergency Contraception
5. Pregnancy and Pregnancy Testing

Counseling A Potentially Pregnant Patient

If a patient expresses concern that she may be pregnant, tell her to stop taking isotretinoin immediately and call her prescriber.

Males And Birth Defects

Unlike in female patients, there is no pattern of birth defects in babies whose fathers were taking isotretinoin. Approximately 3 to 5 babies in 100 (3% to 5%) are born with some kind of birth defect from other causes, not from isotretinoin.[2]

Isotretinoin also has not been shown to affect a male's ability to father children. Studies did not show effects on sperm count, how sperm look, or how well they swim and move. (For more information, see page 4.)

REFERENCES

1 Dai WS, Hsu M-A, ltri LM Safety of pregnancy after discontinuation of isotretinoin *Arch Dermatol* 1989;125:362-355

2 Centers for Disease Control and Prevention Birth defects: frequently asked questions Available at: http //www.cdc.gov/ncbddd/bd/faq1.htm#Whatisabirthdefect Accessed August 8, 2005

For More Information About Isotretinoin

To get information about specific brands of isotretinoin, the contact information for individual makers can be obtained by calling 1-866-495-0654 or via www.ipledgeprogram.com.

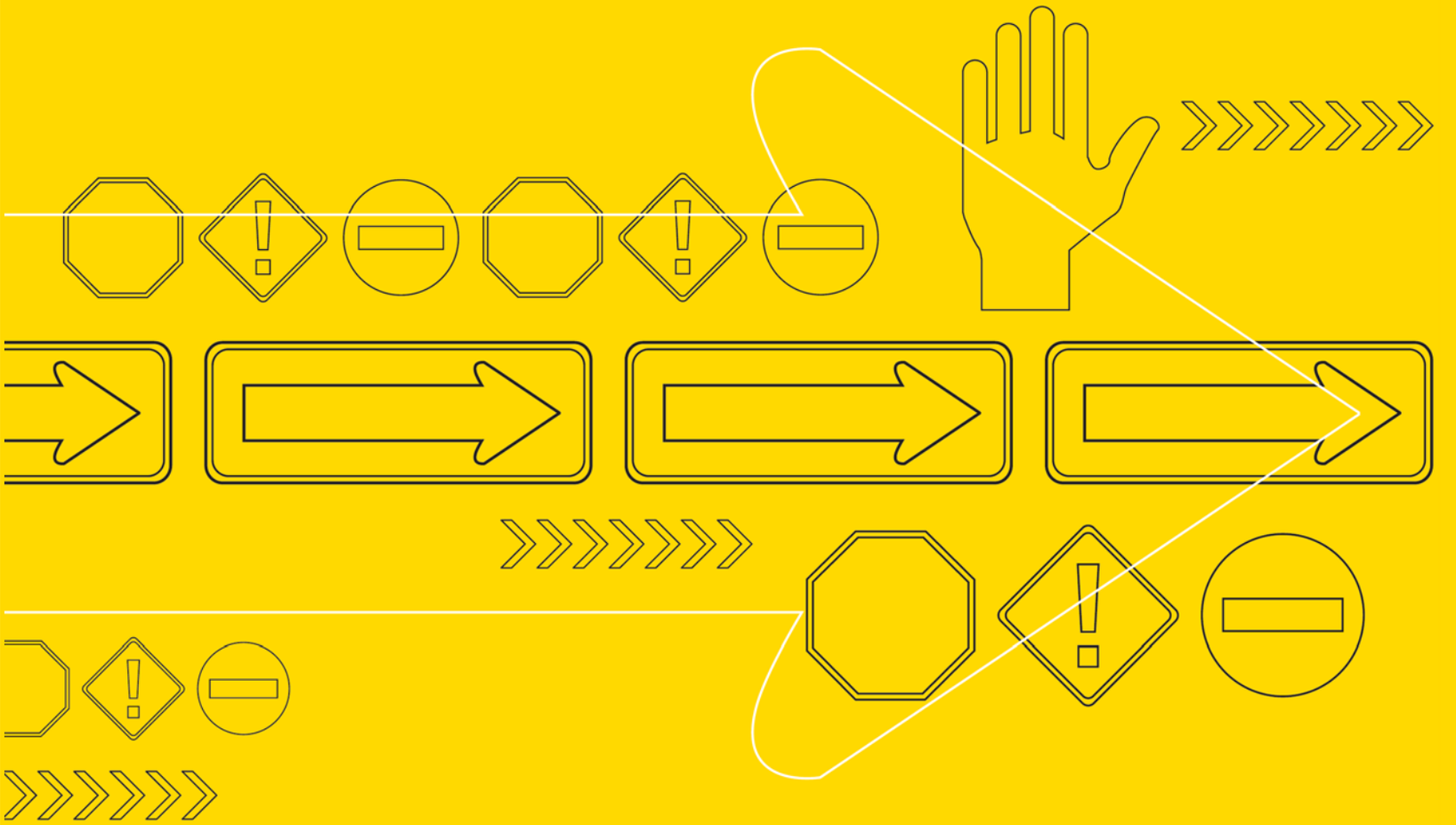
For iPLEDGE Program Information

Call Center hours: Monday through Saturday, 9AM–12AM (midnight) EST

1-866-495-0654

www.ipledgeprogram.com

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS.**



www.ipledgeprogram.com 1-866-495-0654

Isotretinoin must not be used by female patients who are or may become pregnant. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking isotretinoin in any amount, even for a short period of time. Potentially any fetus exposed during pregnancy can be affected. There are no accurate means of determining whether an exposed fetus has been affected.

IMPORTANT NOTICE

Use only isotretinoin products approved by the US Food and Drug Administration.

Obtain isotretinoin prescriptions *only* from pharmacies that are licensed in the United States and are registered with and activated in the iPLEDGE Program.

iPLEDGE™

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